

**AMENDMENTS TO THE CLAIMS**

The following Listing of the Claims will replace all prior versions and all prior listings of the claims in the present application:

Listing of The Claims:

Claims 1 - 16 (Currently cancelled)

17. (Currently Amended) A polypeptide pair comprising a first polypeptide immobilized to a support, and a second binding partner polypeptide bound to the first polypeptide, wherein the binding of the polypeptides to each other is detectable, and covalent modification of at least one of the polypeptides results in modulation of the binding, and is required for said association of said first polypeptide and said second binding partner polypeptide, wherein said second binding partner polypeptide is not a phospho-specific antibody, and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, ~~geranylation~~, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation and the reversal of these covalent modifications.

18. (Currently amended) A method for detecting or monitoring the activity of a modulator of a polypeptide modifying agent, comprising the steps of:

providing a first polypeptide, and a second polypeptide, wherein at least one of the polypeptides is susceptible to modification, and the first and second polypeptides are capable of binding to each other, and covalent modification of one or both of the polypeptides by the modifying agent in the presence of a modifying group substrate results in modulation of the binding of the polypeptides to each other;

allowing the polypeptides to bind to each other;

contacting the polypeptides with a modifying agent in the presence of said modifying group substrate;

detecting modulation of the binding of the polypeptides to determine a reference signal modulation,

contacting the polypeptides with a modifying agent and a candidate modulator of the modifying agent, and

detecting modulation of binding of the polypeptides in the presence of said candidate modulator, and comparing the modulation detected in the presence of said candidate modulator with the reference signal modulation.

19. (Cancelled)

20. (Currently cancelled)

21. (Currently Amended) A method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a first polypeptide, the method comprising the steps of:

a) providing a first polypeptide immobilized on a support, wherein said first polypeptide comprises a binding site to which a second polypeptide specifically binds, wherein said second polypeptide is not a phospho-specific antibody, and wherein covalent modification of said first polypeptide detectably changes the association of said first and second polypeptide;

b) providing said second polypeptide and said test sample in the presence of a modifying group substrate , and contacting said second polypeptide and said test sample with said first polypeptide immobilized on a support;

c) measuring association of said first polypeptide with said second polypeptide; and

d) comparing said association with the association of a first and second polypeptide contacted with a control sample known to contain said modifying enzyme and said modifying group substrate wherein a change in the association of said first and second polypeptide determined in step (c) relative to said association

determined in step (d) provides an indicator of the presence of the enzyme in said test sample.

22. (New) A method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of:
- a) providing a polypeptide pair comprising a first polypeptide and a second, binding partner polypeptide, capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation;
  - b) providing a modifying group substrate, wherein said substrate, in the presence of a modifying enzyme, results in the covalent modification of said first polypeptide or said second binding partner polypeptide;
  - c) immobilizing the first polypeptide to a physical support;
  - d) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample and said modifying group substrate; and
  - e) measuring the association of the second, binding partner polypeptide to the first polypeptide, thereby determining the covalent modification of at least one of said polypeptides, whereby the presence of said modifying enzyme is detected.
23. (New) A method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of:
- a) providing a polypeptide pair comprising a first polypeptide and a covalently modified second, binding partner polypeptide capable of associating with said first polypeptide, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said association of the polypeptides is detectable, and wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association and wherein said covalent

modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation;

b) immobilizing the first polypeptide to a physical support;

c) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample; and

d) measuring the association of the second, binding partner polypeptide to the first polypeptide, thereby determining the removal of said covalent modification from said second binding partner polypeptide, whereby the presence of said modifying enzyme is detected.

24. (New) The method of claim 22 or 23, wherein at least one of the polypeptides is labeled.

25. (New) The method of claim 24, wherein said label comprises a fluorescent label.

26. (New) The method of claim 24, wherein said label comprises a radioactive label.

27. (New) The method of claim 22 or 23, wherein both the immobilized polypeptide and the binding partner polypeptide are labeled.

28. (New) The method of claim 27, wherein said label on said immobilized polypeptide is different from said label on said second, binding partner polypeptide.

29. (New) The method of claim 27, wherein a detectable signal is generated by an interaction between the label on said immobilized polypeptide and the label on said binding partner polypeptide.

30. (New) The method of claim 29, wherein said interaction comprises energy transfer.

31. (New) The method of claim 22 or 23, wherein said association is measured by monitoring the molecular mass of the binding partner polypeptide in association with the first polypeptide.

32. (New) The method of claim 31, wherein said association is measured by surface plasmon resonance.
33. (New) The method of claim 31, wherein said association is measured by scintillation proximity assay.
34. (New) A method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method consisting of the steps, in the sequence set forth of:
- a) providing a polypeptide pair comprising a first polypeptide and a second, binding partner polypeptide capable of associating, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation;
  - b) providing a modifying group substrate, wherein said substrate, in the presence of a modifying enzyme, results in the covalent modification of said first polypeptide or said second binding partner polypeptide;
  - c) immobilizing the first polypeptide to a physical support;
  - d) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample and said modifying group substrate; and
  - e) measuring the association of the second, binding partner polypeptide to the first polypeptide, by contacting said binding partner polypeptide with an antibody that binds to said binding partner polypeptide, thereby determining the covalent modification of at least one of said polypeptides, whereby the presence of said modifying enzyme is detected.
35. (New) A method for detecting, in a sample, the presence of a modifying enzyme which covalently modifies a polypeptide, the method comprising the steps of, in the sequence set forth:

- a) providing a polypeptide pair comprising a first polypeptide and a covalently modified second, binding partner polypeptide capable of associating, wherein said second, binding partner polypeptide is not a phospho-specific antibody, and wherein said association of the polypeptides is detectable, and wherein removal of the covalent modification from said second, binding partner polypeptide by a modifying enzyme results in modulation of the association and wherein said covalent modification comprises one of the group consisting of phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinization, ADP-ribosylation;
  - b) immobilizing the first polypeptide to a physical support;
  - c) contacting said immobilized polypeptide and said second binding partner polypeptide in the presence of said sample; and
  - d) measuring the association of the second, binding partner polypeptide to the first polypeptide, using an antibody that binds to said binding partner polypeptide, thereby determining the removal of said covalent modification from said second binding partner polypeptide, whereby the presence of said modifying enzyme is detected.
36. (New) The method of claim 22 or 23, comprising the additional step, prior to step (e), of contacting one or both of said first polypeptide and said binding partner polypeptide with an agent capable of modifying one or both of said polypeptides.
37. (New) The method of claim 23, wherein the immobilized polypeptide is the polypeptide which is covalently modified.
38. (New) The method of claim 22 or 23, wherein said association is measured in real time.
39. (New) The method of claim 22, wherein said step (e) comprises assaying a modification selected from the group consisting of: proteolysis, phosphorylation, acylation, glycosylation, ubiquitination, prenylation, sentrinisation, and ADP-ribosylation.
40. (New) The method of claim 23, wherein said step (e) comprises assaying the reversal of a modification selected from the group consisting of: proteolysis, phosphorylation,

acylation, glycosylation, ubiquitination, prenylation, sentrinisation, and ADP-ribosylation.